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RNA aptamers for capturing early species of aberrant protein aggregates in neurodegenerative diseases

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Aptamers are short, single-stranded oligonucleotide sequences capable of binding specific protein targets with high affinity and selectivity, representing a promising tool for both diagnostics and therapeutics. This work illustrates the rational design of de-novo RNA aptamers able to recognize efficiently their protein target at all stages of its maturation to full aggregate species. TDP-43, an essential RNA-binding protein whose aberrant aggregation are associated with up to 97% of sporadic cases of amyotrophic lateral sclerosis (ALS), was selected as target. *In vitro* validation of the binding strength of the RNA aptamers towards TDP-43 identified binding constants in the nM scale. In association with super-resolution microscopy, the RNA aptamers were employed to successfully visualize all oligomeric state of TDP-43 *in vitro*, from the smallest oligomeric species to largest aggregates. Transfection of the aptamers in mammalian cellular models recapitulating ALS phenotype demonstrated that they co-localize with both soluble and aggregated TDP-43 in a precise and selective manner. The employment of the RNA aptamers to stain TDP-43 inclusions in ALS patients' cortical sections allowed for the identification of aggregates as small as 10 nm and for the definition their size and shape. The high specificity of targeting renders the RNA aptamers designed in such fashion a tool with extremely high potential in the diagnostic of proteinopatic diseases at the earliest stages of the development.

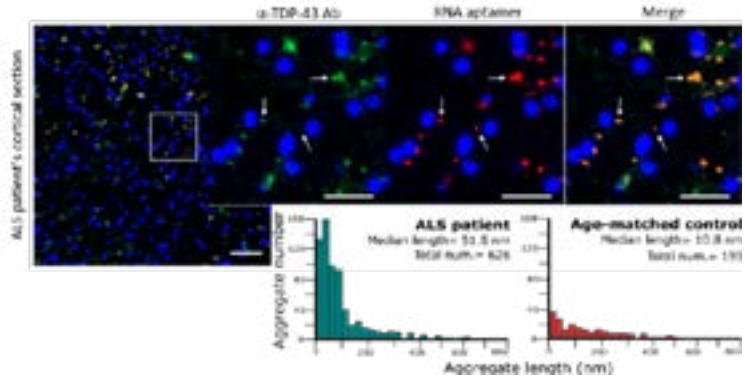

Figure: Visualization of TDP-43 aggregates by means of RNA aptamers in cortical sections of the brain of ALS patients.

Compared to an anti-TDP-43 antibody (green), the RNA aptamer (red) can identify more precisely and specifically TDP-43 aggregates. The RNA aptamers can also be employed to count the number and define the size of such aggregates in ALS patients compared to age-matched controls.

Biography

Elsa Zacco research focus is the investigation of the effect of RNA in protein phase separation. My interest sparkled during my post-doc at King's College London, when I specialized in the investigation of protein aggregation and the role that RNA may play in it. My research supports the thesis that RNA plays a central role at post-transcriptional regulation and often determines the fate of ribonucleoprotein complexes. My expertise is to investigate the structural-functional interplay between proteins and RNA and unveiling the molecular mechanisms of their interactions. I am currently a senior Marie Curie research fellow at the Italian Institute of Technology, where I am addressing my expertise towards dysfunction of protein-RNA interactions in neurological disorders.